International Application No PCT/GB2004/005156

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N5/06 A61K47/48 A61K49/18 A61K41/00 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C12N A61K Documentation searched other than minimum documentation to the extent that such documents are included. In the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, INSPEC C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category ° 1 - 30LEWIN M ET AL: "Tat peptide-derivatized Х magnetic nanoparticles allow in vivo tracking and recovery of progenitor cells" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 18, April 2000 (2000-04), pages 410-414, XP002958421 ISSN: 1087-0156 abstract page 411 - page 412 WO 02/051985 A (KEELE UNIVERSITY; EL-HAJ, 1-30 Х ALICIA, JENNIFER, HAFEEZA; DOBSON, JON, PAUL) 4 July 2002 (2002-07-04) page 4 claims 1-13 -/--Patent family members are listed in annex. Further documents are listed in the continuation of box C. Х "T" later document published after the international filing date or priority date and not in conflict with the application but died to understand the principle or theory underlying the Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to Involve an inventive step when the document is taken alone "E" earlier document but published on or after the international "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) comment or particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Y" document of particular relevance; the claimed invention "O" document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search 0 6. 04. 2006 21 December 2005 Authorized officer Name and mailing address of the ISA Buropean Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Dullaart, A Fax: (+31-70) 340-3016

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International Application No PCT/GB2004/005156

| C.(Continua | ation) DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                                                                                                                                         | PC1/G52004/003136     |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category °  | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                 | Relevant to claim No. |
| X           | CARTMELL S H ET AL: "Development of magnetic particle techniques for long-term culture of bone cells with intermittent mechanical activation"  IEEE TRANSACTIONS ON NANOBIOSCIENCE, IEEE SERVICE CENTER, PISCATAWAY, NY, US, vol. 1, no. 2, June 2002 (2002-06), pages 92-97, XP001152893  ISSN: 1536-1241  abstract page 93, left-hand column, paragraph METHODOLOGY - page 94, left-hand column, | 1-30                  |
| X           | paragraph RESULTS  FROHLICH M W ET AL: "Ex Vivo Activation and Expansion of T Cells from the Peripheral Blood of Multiple Myeloma Patients Using the XcellerateTM Process" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, US, vol. 100, no. 11, 16 November 2002 (2002-11-16), XP002296916 ISSN: 0006-4971 abstract no. 5259 the whole document                                                         | 1-30                  |
| X           | CARTMELL S H ET AL: "Development of magnetic particle techniques for long-term culture of bone cells with intermittent mechanical activation"  IEEE TRANSACTIONS ON NANOBIOSCIENCE IEEE USA, vol. 1, no. 2, June 2002 (2002-06), pages 92-97, XP011077118  ISSN: 1536-1241  abstract page 93, paragraph METHODOLOGY - page 94, right-hand column                                                   | 1-30                  |
| X           | WO 02/32397 A (VIRGINIA COMMONWEALTH UNIVERSITY INTELLECTUAL PROPERTY FOUNDATION; SIM) 25 April 2002 (2002-04-25) page 42 examples claims                                                                                                                                                                                                                                                          | 1-30                  |
| Х,Р         | WO 2004/000369 A (KEELE UNIVERSITY; EL HAJ, JENNIFER, ALICIA; DUBSON, JON, PAUL) 31 December 2003 (2003-12-31) cited in the application the whole document                                                                                                                                                                                                                                         | 1-30                  |

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International application No. PCT/GB2004/005156

| Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)                                                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:                                                                                                                                           |
| 1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:                                                                                                                                                                     |
| Although claims 89-112 are directed to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the compound/composition.                                                                                                    |
| 2. X Claims Nos.: 204-205 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  See FURTHER INFORMATION sheet PCT/ISA/210 |
| 3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).                                                                                                                                            |
| Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)                                                                                                                                                                                   |
| This International Searching Authority found multiple inventions in this international application, as follows:                                                                                                                                                                    |
| see additional sheet                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                    |
| 1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.                                                                                                                                        |
| 2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.                                                                                                                            |
| As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:                                                                               |
| No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  1-30 in part                                                     |
| Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.                                                                                                                          |

Continuation of Box II.1

Although claims 89-112 are directed to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 204-205

The present application contains 205 claims, of which 12 are independent. There is no clear distinction between the independent claims because of overlapping scope. There are so many claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as it is particularly burdensome for a skilled person to establish the subject-matter for which protection is sought. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19 and 9.25).

Claims 204-205 do not define the scope for which protection is sought in technical terms, which would allow them to be distinguishable over general ideas in the prior art. Therefore, these claims cannot be searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-30 in part

Selective activation of stem cells as claimed.

2. claims: 1-30 in part

Selective targeting of stem cells as claimed.

3. claims: 31-88

Magnetic manipulation of stem cells as claimed.

4. claims: 89-109,111 and 202

Method of treating a patient as claimed.

5. claim: 110

Method of inducing a therapeutic effect in a stem cell as claimed.

6. claim: 112

Method of targeting a therapeutically active agent to a stem cell as claimed.

7. claims: 113-143

Magnetic manipulation of a stem cell as claimed.

8. claims: 144-201

The manufacture of a therapy as claimed.

9. claim: 203

Method of targeting a therapeutically active agent to a cell as claimed.

Information on patent family members

PCT/GB2004/005156

| Patent document cited in search report |   | Publication date |                            | Patent family member(s)                                           | Publication date                                                   |
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| WO 0232397                             | A | 25-04-2002       | AU<br>EP<br>JP             | 2438702 A<br>1333808 A2<br>2004532802 T                           | 29-04-2002<br>13-08-2003<br>28-10-2004                             |
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International Application No PCT/GB2004/005156

| A. CLASSIF                                                                                                                                                                                                                                  | CATION OF SUBJECT                                                                   | MATTER                      | AC11//1 /0                 | <u> </u>         | Λ61V/10/19                         |                        |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------|----------------------------|------------------|------------------------------------|------------------------|--|
| INV. C                                                                                                                                                                                                                                      | 12N5/06                                                                             | A61K47/48                   | A61K41/0                   | שו               | A61K49/18                          |                        |  |
|                                                                                                                                                                                                                                             |                                                                                     |                             |                            |                  |                                    |                        |  |
|                                                                                                                                                                                                                                             | International Patent Class                                                          | sification (IPC) or to both | national classificati      | ion and IPC      | ·                                  |                        |  |
| B. FIELDS S                                                                                                                                                                                                                                 | SEARCHED<br>cumentation searched (cl                                                | assification system folio   | wed by classification      | n symbols)       |                                    |                        |  |
|                                                                                                                                                                                                                                             | A61K                                                                                | ussmoution by storm rone    | ,,                         | ,                |                                    |                        |  |
|                                                                                                                                                                                                                                             |                                                                                     |                             |                            |                  |                                    |                        |  |
| Documentati                                                                                                                                                                                                                                 | on searched other than m                                                            | ninimum documentation       | to the extent that su      | ch docume        | nts are included. In the fields se | arched                 |  |
| •                                                                                                                                                                                                                                           |                                                                                     |                             |                            |                  |                                    |                        |  |
| Electronic da                                                                                                                                                                                                                               | ta base consulted during                                                            | the international search    | n (name of data base       | e and, whe       | re practical, search terms used)   |                        |  |
| EPO-Int                                                                                                                                                                                                                                     | ternal, INSPE                                                                       | C                           |                            |                  |                                    |                        |  |
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|                                                                                                                                                                                                                                             |                                                                                     |                             |                            |                  |                                    |                        |  |
|                                                                                                                                                                                                                                             | NTS CONSIDERED TO Citation of document, w                                           |                             | propriete of the rele      | want nassa       | nes                                | Relevant to claim No.  |  |
| Category °                                                                                                                                                                                                                                  | Citation of document, w                                                             |                             | Propriete, or are rele     |                  | <b>u</b>                           |                        |  |
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|                                                                                                                                                                                                                                             | magnetic n                                                                          | anoparticles<br>nd recovery | allow in v                 | /ivo             |                                    |                        |  |
|                                                                                                                                                                                                                                             | tracking a                                                                          | na recovery<br>TECHNOLOGY,  | NATURE PUBL                | LISHIN           | G,                                 |                        |  |
|                                                                                                                                                                                                                                             | US.                                                                                 |                             |                            |                  |                                    |                        |  |
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|                                                                                                                                                                                                                                             | ISSN: 1087                                                                          |                             |                            |                  |                                    |                        |  |
|                                                                                                                                                                                                                                             | abstract<br>page 411 -                                                              | nage 412                    |                            |                  |                                    |                        |  |
|                                                                                                                                                                                                                                             | · -                                                                                 |                             |                            | . =1 0           | A 7                                | 1-30                   |  |
| X                                                                                                                                                                                                                                           | WO 02/0519                                                                          | 85 A (KEELE<br>NNIFER, HAFE | UNIVERSITY;<br>F7A: DOBSON | ; EL-H<br>N. JON | AU,                                | 1-30                   |  |
| İ                                                                                                                                                                                                                                           | PAUL) 4 Ju                                                                          | ly 2002 (200                | 2-07-04)                   |                  | •                                  |                        |  |
|                                                                                                                                                                                                                                             | page 4<br>claims 1-1                                                                |                             |                            |                  |                                    |                        |  |
|                                                                                                                                                                                                                                             | Claims 1-1                                                                          | .J<br>                      |                            |                  |                                    |                        |  |
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| X Furt                                                                                                                                                                                                                                      | her documents are listed                                                            | in the continuation of b    | ox C.                      | Х                | atent family members are listed    | in annex.              |  |
| ° Special ca                                                                                                                                                                                                                                | tegories of cited docume                                                            | nts:                        |                            | "T" later d      | ocument published after the int    | ernational filing date |  |
| "A" document defining the general state of the art which is not considered to be of particular relevance or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |                                                                                     |                             |                            |                  |                                    |                        |  |
| "E" earlier document but published on or after the international  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to                                                         |                                                                                     |                             |                            |                  |                                    |                        |  |
| "L" document which may throw doubts on priority claim(s) or  "L" document which is clied to establish the publication date of another  "Y" document of particular relevance; the claimed invention                                          |                                                                                     |                             |                            |                  |                                    |                        |  |
| citation or other special reason (as specified)  cannot be considered to involve an inventive step when the countries combined with one or more other such docu-                                                                            |                                                                                     |                             |                            |                  |                                    |                        |  |
| other means in the art.                                                                                                                                                                                                                     |                                                                                     |                             |                            |                  |                                    |                        |  |
| Date of the actual completion of the international search  Date of mailing of the international search                                                                                                                                      |                                                                                     |                             |                            |                  |                                    |                        |  |
| n 6 na 2006                                                                                                                                                                                                                                 |                                                                                     |                             |                            |                  |                                    |                        |  |
| 7                                                                                                                                                                                                                                           | 21 December 2005                                                                    |                             |                            |                  |                                    |                        |  |
| Name and                                                                                                                                                                                                                                    | Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2 |                             |                            |                  |                                    |                        |  |
|                                                                                                                                                                                                                                             | NL - 2280 HV Riist                                                                  | NIK                         | 2W1 E                      |                  | Dullaset A                         |                        |  |
| Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016                                                                                                                                                                        |                                                                                     |                             |                            |                  | Dullaart, A                        |                        |  |

International Application No PCT/GB2004/005156

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                   | Relevant to claim No. |
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| X          | CARTMELL S H ET AL: "Development of magnetic particle techniques for long-term culture of bone cells with intermittent mechanical activation"  IEEE TRANSACTIONS ON NANOBIOSCIENCE, IEEE SERVICE CENTER, PISCATAWAY, NY, US, vol. 1, no. 2, June 2002 (2002-06), pages 92-97, XP001152893  ISSN: 1536-1241  abstract page 93, left-hand column, paragraph METHODOLOGY - page 94, left-hand column, paragraph RESULTS | 1-30                  |
| X          | FROHLICH M W ET AL: "Ex Vivo Activation and Expansion of T Cells from the Peripheral Blood of Multiple Myeloma Patients Using the XcellerateTM Process" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, US, vol. 100, no. 11, 16 November 2002 (2002-11-16), XP002296916 ISSN: 0006-4971 abstract no. 5259 the whole document                                                                                              | 1-30                  |
| X          | CARTMELL S H ET AL: "Development of magnetic particle techniques for long-term culture of bone cells with intermittent mechanical activation"  IEEE TRANSACTIONS ON NANOBIOSCIENCE IEEE USA, vol. 1, no. 2, June 2002 (2002-06), pages 92-97, XP011077118  ISSN: 1536-1241 abstract page 93, paragraph METHODOLOGY - page 94, right-hand column                                                                      | 1-30                  |
| X          | WO 02/32397 A (VIRGINIA COMMONWEALTH UNIVERSITY INTELLECTUAL PROPERTY FOUNDATION; SIM) 25 April 2002 (2002-04-25) page 42 examples claims                                                                                                                                                                                                                                                                            | 1-30                  |
| Х,Р        | WO 2004/000369 A (KEELE UNIVERSITY; EL HAJ, JENNIFER, ALICIA; DUBSON, JON, PAUL) 31 December 2003 (2003-12-31) cited in the application the whole document                                                                                                                                                                                                                                                           | 1-30                  |

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International application No. PCT/GB2004/005156

| Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)                                                                                                                                                                           |     |
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| This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:                                                                                                                                           |     |
| 1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:                                                                                                                                                                     |     |
| Although claims 89-112 are directed to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effe of the compound/composition.                                                                                                       | cts |
| 2. X Claims Nos.: 204-205 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  See FURTHER INFORMATION sheet PCT/ISA/210 |     |
|                                                                                                                                                                                                                                                                                    |     |
| 3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).                                                                                                                                            |     |
| Box III Observations where unity of invention is tacking (Continuation of item 3 of first sheet)                                                                                                                                                                                   |     |
| This International Searching Authority found multiple inventions in this international application, as follows:                                                                                                                                                                    |     |
| see additional sheet                                                                                                                                                                                                                                                               |     |
|                                                                                                                                                                                                                                                                                    |     |
| 1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.                                                                                                                                        |     |
| As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.                                                                                                                               |     |
|                                                                                                                                                                                                                                                                                    | •   |
| 3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:                                                                            |     |
|                                                                                                                                                                                                                                                                                    |     |
| ·                                                                                                                                                                                                                                                                                  |     |
| 4. No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:                                                                |     |
| 1-30 in part                                                                                                                                                                                                                                                                       |     |
|                                                                                                                                                                                                                                                                                    |     |
| Remark on Protest The additional search fees were accompanied by the applicant's protest.                                                                                                                                                                                          |     |
| No protest accompanied the payment of additional search fees.                                                                                                                                                                                                                      |     |
|                                                                                                                                                                                                                                                                                    |     |

Continuation of Box II.1

Although claims 89-112 are directed to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 204-205

The present application contains 205 claims, of which 12 are independent. There is no clear distinction between the independent claims because of overlapping scope. There are so many claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as it is particularly burdensome for a skilled person to establish the subject-matter for which protection is sought. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19 and 9.25).

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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-30 in part

Selective activation of stem cells as claimed.

2. claims: 1-30 in part

Selective targeting of stem cells as claimed.

3. claims: 31-88

Magnetic manipulation of stem cells as claimed.

4. claims: 89-109,111 and 202

Method of treating a patient as claimed.

5. claim: 110

Method of inducing a therapeutic effect in a stem cell as claimed.

6. claim: 112

Method of targeting a therapeutically active agent to a stem cell as claimed.

7. claims: 113-143

Magnetic manipulation of a stem cell as claimed.

8. claims: 144-201

The manufacture of a therapy as claimed.

9. claim: 203

Method of targeting a therapeutically active agent to a cell as claimed.

Information on patent family members

PCT/GB2004/005156

| Patent document Publication cited in search report date |   | ,          | . Patent family<br>member(s) | Publication<br>date                                             |                                          |
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